UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/831,061 | 08/31/2001 | Jean-Yves Bonnefoy | PF86PCTSEQ | 1138 |

7590 08/29/2003

G Patrick Sage
The Firm of Hueschen & Sage
500 Columbia Plaza
350 East Michigan Avenue
Kalamazoo, MI 49007-3856

| EXAMINER |
|---|
| DEVI, SARVAMANGALA J N |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | 17 |

DATE MAILED: 08/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/831,061 | Bonnefoy et al. |
| **Examiner** | **Art Unit** |
| S. Devi, Ph.D. | 1645 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Jun 2, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *25-48* is/~~are~~ pending in the application.

4a) Of the above, claim(s) *40-48* is/~~are~~ withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25-39* is/~~are~~ rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 08/31/01 (paper no. 8).

### Election

2) Acknowledgment is made of Applicants' election filed 06/02/03 (paper no. 3) in response to the written lack of unity mailed 04/23/03 (paper no. 9). Applicants have elected invention I, claims 25-39, with traverse. Because Applicants did not distinctly and specifically point out the supposed errors in the lack of unity, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)).

### Status of Claims

3) Claims 1-24 have been canceled via the preliminary amendment filed 05/04/01.

New claims 25-48 have been added via the preliminary amendment filed 05/04/01.

Claims 25-48 are pending.

Claims 40-48 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Elected claims 25-39 are under examination.

### Sequence Listing

4) Acknowledgment is made Applicants' submission of the CRF and the Sequence Listing. The CRF error, i.e., non-ASCII 'garbage' at the beginning/end of the file has been corrected by the STIC Systems Branch and the Sequence Listing has been entered.

### Priority

5) The instant application is a national stage 371 application of PCT/FR99/02734, filed 11/08/1999 and claims priority to application 98/14007 filed 11/06/1998 in France. It is noted that a copy of the non-translated foreign priority document, 98/14007, has been submitted.

### Co-pending Applications

6) At the time this Office Action was written, several co-pending applications related to this case were not available to the Examiner of record for review, for example, SN 09/913,772 and 09/913,107. Applicants' assistance is requested in providing the Office with a copy of the pending claims from the co-pending applications. Applicants are advised that any pending or allowed

applications claiming the instantly claimed composition may serve as a ground for a double patenting rejection in the next Office Action.

**Drawings**

**7)** The drawings are objected to under 37 C.F.R 1.84 because of the reasons set forth by the Draftsperson in the attached Form PTO 948 (paper no. 11). Correction is required.

**Specification - Informalities**

**8)** The instant specification is objected to:

(A) The instant application is informal in the format or arrangement of the specification. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicants' use.

Content of Specification

(a) Title of the Invention: See 37 C.F.R 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 C.F.R 1.78 and M.P.E.P § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See M.P.E.P § 310.

(d) Reference to a "Microfiche Appendix": See 37 C.F.R 1.96(c) and M.P.E.P § 608.05. The total number of microfiche and the total number frames should be specified.

(e) Background of the Invention: The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 C.F.R 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(g) Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 C.F.R 1.74.

(h) Detailed Description of the Invention: A description of the preferred embodiment(s) of the invention as required in 37 C.F.R 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention." Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(i) Claim or Claims: See 37 C.F.R 1.75 and M.P.E.P § 608.01(m). The claim or claims must commence on separate sheet. (37 C.F.R 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps.

(j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single

paragraph of 250 words or less on a separate sheet following the claims.

(k) Drawings: See 37 C.F.R 1.81, 1.83-1.85, and M.P.E.P § 608.02.

(l) Sequence Listing: See 37 C.F.R 1.821-1.825.

(B) The use of the trademarks in the instant specification has been noted in this application. For example, see page 14, lines 18, 29 and 28; and page 15, lines 11, 16, 31, 33, 34 and 37: 'Zwittergent 3-14'; page 17, lines 16, 26, 28, 33 and 34; page 18, line 39; page 19, lines 3, 5, 13, 24 and 29; and page 20, line 6: 'Alexa488'. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

**Rejection(s) under 35 U.S.C. § 112, First Paragraph**

9) Claims 25-39 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the OmpA protein, or a fragment or 80% homologous variant thereof, recited in the claimed method does not exist independent of its function, i.e., the ability to be internalized into or the ability to specifically bind to the antigen-presenting cells. The specification discloses vaccine applications for the OmpA composition produced. However, the instant specification fails to teach a single variant of a OmpA sequence having at least 80% homology to the amino acid sequence of SEQ ID NO: 2 and concurrently having the ability to be internalized into or the ability to specifically bind to the antigen-presenting cells. Vaccine applications minimally require a specific interaction with host's antigen-presenting cells. The precise structure or relevant identifying characteristics of each DNA molecule that encodes a variant OmpA polypeptide having at least 80% identity to the amino acid sequence of SEQ ID NO: 2 and the ability to be internalized into or the ability to specifically bind to the antigen-presenting cells can only be determined empirically by actually making every DNA molecule that encodes the polypeptide of the recited variability, i.e., the instantly recited at least 80% sequence homology, and testing each varied DNA molecule to

determine whether it encodes the at least 80% modified OmpA variant having the particularly disclosed functional activity. There is lack of written description as to which specific at least 5 amino acid-long fragment of the amino acid sequence of SEQ ID NO: 2 is encompassed in the claimed protein fragment. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention or the method includes the use of an amino acid sequence having at least 80% homology to the amino acid sequence of SEQ ID NO: 2 is insufficient to meet the adequate written description requirement of the claimed invention. The amino acid sequence of SEQ ID NO: 2 has specific biologic properties dictated by the structure of the polypeptide and the corresponding structure of the structural gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the polypeptide encoded, and the function of the encoded polypeptide. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the at least 80% modified polypeptide variant. Applicants have not shown that variation or modification of a reference sequence encoding a reference polypeptide as claimed would automatically predict the production of a polypeptide having the recited functional activity. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of DNA molecules encoding a representative number of species of OmpA variants of at least 80% sequence identity as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of an OmpA of SEQ ID NO: 2, a skilled artisan cannot envision the detailed chemical structure of all the polypeptide variant species encompassed by the recited molecule. *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111* states that Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, is for purposes of the 'written description' inquiry, whatever is now claimed." See page 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." See page 1116 of *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111*. Applicants should also note that *Vas-*

*Cath Inc. V. Mathukar, 19 USPQ2d 1111* makes clear that the written description provision of 35 U.S.C § 112, first paragraph, is severable from its enablement provision. See page 1115. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that its is a part of the invention. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016*. The claims are viewed as not meeting the written description provision of 35 U.S.C § 112, first paragraph.

**10)** Claims 25-39 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a process of using a *Klebsiella pneumoniae* OmpA protein having the amino acid sequence of SEQ ID NO: 2 in the preparation of a composition wherein the OmpA has the ability to internalize into dendritic cells, or bind specifically to dendritic cells, monocytes or B lymphocytes, does not reasonably provide enablement for a method of using a *Klebsiella pneumoniae* OmpA protein fragment of any size or a size of at least 5 amino acids, or an amino acid sequence having at least 80% homology with the amino acid sequence of SEQ ID NO: 2 as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the method requires using an OmpA protein variant having at least 80% homology with SEQ ID NO: 2, or an at least 5 amino acid-long fragment of the OmpA protein having the ability to be internalized into the antigen-presenting cells, or the ability to bind specifically to antigen-presenting cells. In other words, the recited protein fragment, or the protein variant

having at least 20% dissimilarity with the amino acid sequence of SEQ ID NO: 2 is *required* to have the recited specific binding and internalizing activities. However, the instant specification does not teach how to make an OmpA fragment or variant of the amino acid sequence SEQ ID NO: 2 with 20% of its amino acids varied or modified in such a way that the resultant variant still maintains the recited functional activity. Neither the specification nor the art discloses an OmpA variant that is at least 20% non-identical to the amino acid sequence of SEQ ID NO: 2 which variant retains the specific binding and internalizing activities. The instant specification fails to demonstrate that an OmpA variant having at least 80% identity to SEQ ID NO: 2, if prepared by one of skill in the art, would retain all the functional or biological properties of the native OmpA protein of SEQ ID NO: 2. It should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. The precise structural composition of the claimed protein fragment or variant is not disclosed, without which one of ordinary skill in the art cannot make and use the claimed product in the claimed method without undue experimentation. The specification lacks disclosure as to how to produce a polypeptide variant having at least 80% sequence identity to SEQ ID NO: 2 and at the same time having all the recited or necessary functions for use in the claimed method. There is no evidence within the instant specification showing that the recited OmpA variant having an amino acid sequence which is "at least 80%" identity to the amino acid sequence of SEQ ID NO: 2, does in fact have the recited activities. There is no predictability that such a protein variant having as much as 20% dissimilarity with the polypeptide of SEQ ID NO: 2, would remain functional for use in a composition. This is critical because the art reflects sensitivity of proteins or polypeptides to alteration of even a single amino acid residue in its amino acid sequence. An alteration in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similar teachings are provided by Lazar *et al* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) who showed that in the protein, transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. In the instant case, it is unlikely that an OmpA

molecule having as much as 20% dissimilarity with the native OmpA of SEQ ID NO: 2 as recited, would have its primary, secondary or tertiary structure unchanged and would have the recited functional activity retained. The effects of such a high dissimilarity upon the protein structure and function are unpredictable. One of skill in the art cannot predict that such an OmpA variant would have its immunologic or biologic specificity. Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al* also taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function(s) is limited. Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein or polypeptide, with as much as 20% dissimilarity to the OmpA protein of SEQ ID NO: 2, the specific binding or the internalizing activity of the claimed OmpA variant could not be predicted, based solely on the sequence identity, nor would it be expected to be the same as that of the OmpA protein of SEQ ID NO: 2. For example, if one nucleotide in the nucleotide sequence that encodes the OmpA of SEQ ID NO: 2 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native OmpA of SEQ ID NO: 2. There is no certainty that amino acid substitutions at any position would yield an OmpA protein that retains the function and/or the specificity of the native OmpA protein. The specification fails to demonstrate that an OmpA protein having 20% structural dissimilarity to SEQ ID NO: 2 would be functionally equivalent to the native OmpA of SEQ ID NO: 2, particularly with regard to the specific binding or the internalizing

activities. One simply cannot predict what effects a given deletion, insertion or modification in the amino acid sequence would cause, and therefore such modified molecules are not enabled as Applicants' invention. Applicants have not enabled the full scope of the invention as claimed for those OmpA molecules which are altered or varied, or for OmpA fragments at least 5 amino acid-long. The specification only discloses a *Klebsiella pneumoniae* OmpA protein of SEQ ID NO: 2. Undisclosed and unidentified functional OmpA molecules of at least 80% identity encompassed in the claims are not enabled for their scope. Although a skilled artisan might envision making a number of changes in the reference polynucleotide sequence in accordance with Applicants' disclosure, it is highly uncertain that the protein variant as recited would be functionally equivalent to the native OmpA protein of SEQ ID NO: 2. The altered polypeptide would vary in an unknown or unpredictable manner from the disclosed native OmpA sequence. For these reasons, making and using of the instantly claimed protein fragment or variant having the desired function(s) is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the art, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

**Rejection(s) under 35 U.S.C. § 112, Second Paragraph**

**11)** The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

**12)** Claims 25-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 25, 26, 29, 30, 32, 34, 36 and 38 are indefinite in the recitation 'fragment', because it is unclear what is encompassed in this limitation. What constitutes a 'fragment', and how much of the OmpA protein's original structure has to be retained such that the resulting protein can be considered as a'fragment', is not clear. The metes and bounds of the structure encompassed in

the limitation 'fragment' is indeterminate. Does a single amino acid, or a dipeptide qualify as a 'fragment'?

(b) Claim 29 does not recite positive active steps so that the claim sets out and circumscribes particular areas with reasonable degree of precision and particularity and make clear what subject matter the claims encompass, as well as make clear the subject matter from which others would be precluded. See *Ex parte Erlich, 3 USPQ2d 1011 (BPAI, 1987)*. Claims are incomplete because they omit essential steps. There are no steps delineating the claimed method of using an enterobacterium OmpA protein, or a fragment thereof, for preparing a composition.

(c) Claim 25 is confusing in that it is unclear how 'said enterobacterium OmpA protein ... is internalized into the antigen-presenting cells' during the process of using the protein for preparing a composition. Is this process of internalization taking place *in vitro* during the claimed process, or is internalization taking place *in vivo*? Are antigen-presenting cells involved or needed in the preparation of the composition using the OmpA protein? Clarification/correction is requested.

(d) Claims 25, 26 and 29-31 are vague and confusing in the recitation 'enterobacterium', because it is unclear whether this represents a bacterial genus, or a member of the family *Enterobacteriaceae*.

(e) Claim 25 is vague in the recitation 'associated with it', because it is unclear what is encompassed in the term 'it'.

(f) Claim 26 is vague and confusing in the recitation: 'wherein said .... OmpA protein ..... binds specifically to antigen-presenting cells', because it is unclear whether the process of specific binding is to take place *in vivo,* or *in vitro* during the process of using the OmpA in the preparation of a composition.

(g) Claim 32 is vague in the recitation: 'sequence SEQ ID NO: 2' without clearly reciting that the sequence is an amino acid sequence. For clarity, it is suggested that Applicants replace the recitation with --the amino acid sequence of SEQ ID NO: 2--.

(h) Claim 32 is redundant and/or confusing in the recitation: 'b) the amino acid sequence of a sequence'.

(i) Claim 32 lacks proper antecedence for the limitation: 'a sequence as defined in a) or b)'. For proper antecedence, it is suggested that Applicants replace the recitation with --the

sequence as defined in a) or b)--.

(j) Claims 26-39, which depend directly or indirectly from claim 25, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim(s).

**Rejection(s) under 35 U.S.C. § 102**

**13)** The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**14)** Claims 25-39 are rejected under 35 U.S.C. § 102(a) as being anticipated by Adreoni *et al.* (WO 99/49892A2).

The recitations in the last part of claim 25 beginning at 'intended for ...' do not constitute a step of the claimed process of using an enterobacterium OmpA protein or a fragment thereof for preparing a composition. The intended use of the end product of the claimed process, i.e., the composition as recited is not involved in the process of using the OmpA for preparing a composition. Since internalization into the antigen-presenting cells or specific binding to antigen-presenting cells is not a step of the claimed method, this limitation is viewed as an intrinsic property of the recited OmpA. The purpose or the intended use of the composition prepared by the claimed process of using the recited enterobacterium OmpA does not result in a manipulative difference between the claimed invention and the prior art.

Adreoni *et al.* taught a process of using an enterobacterial outer membrane protein A fragment or a *Klebsiella* membrane protein fragment for preparing a pharmaceutical composition for nasal delivery, to improve a mammal's immunity to an antigen or hapten, i.e., a biologically active substance that is associated with it (see abstract and claims). The OmpA protein or its fragment is produced by extraction from an enterobacterial culture or by a recombinant process (see Examples 1 and 2; and claims 4 and 5). The amino acid sequence of the rP40 OmpA is depicted in pages 1 and 2 under 'Liste De Sequences' which meets the description of the amino acid sequence recited in the instant claim 32. The biologically active substance is a peptide, a polysaccharide, a oligosaccharide

or a nucleic acid, which is coupled covalently to the OmpA protein or its fragment via an amino acid linker, i.e., attachment element, such as Cys, aspartic acid or ornithine (see Example 3; and claims 7 and 14-16). The biologically active substance is a recombinant hybrid (i.e., chimeric) protein (see claim 17).

Claims 25-39 are anticipated by Adreoni *et al.*

**15)** Claims 25-35, 38 and 39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Binz *et al.* (WO 9741888-A1).

Binz *et al.* disclosed a method of using the OmpA protein P40 from *Klebsiella pneumoniae* or a fragment or variant thereof having 99.4% sequence or structural identity with the instantly recited amino acid sequence of SEQ ID NO: 2 for preparing an immunogenic composition or a vaccine. Binz's amino acid sequence also qualifies as a fragment of the instant recited amino acid sequence of SEQ ID NO: 2, because it is a truncated SEQ ID NO: 2. See the attached sequence alignment report; and abstract and claims of Binz *et al.* The OmpA protein or a fragment or variant thereof is associated with a biologically active substance, such as, a bacterial oligosaccharide or polysaccharide to protect humans and animals against infection (see Examples 6 and 7), and therefore it is inherent from the disclosure of Binz *et al.* that the prior art composition is intended for specific presentation targeting of the biologically active substance to host's antigen presenting cells, such as, dendritic cells, macrophages or B lymphocytes. The polysaccharide or oligosaccharide is chemically or covalently coupled to the OmpA protein or a fragment thereof. The protein is extracted from a Gram negative bacterial culture, or produced by a recombinant process (see Examples 1-3).

Claims 25-35, 38 and 39 are anticipated by Binz *et al.*

**Objection(s)**

**16)** Claim 31 is objected to for only partial italicization of the limitation: 'Klebsiella *pneumoniae*'.

**Remarks**

**17)** Claims 25-39 stand rejected.

**18)** Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center receives facsimile

transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

**19)** Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER

SEQ ID NO. 2.

RESULT 1
AAR93797
ID AAR93797 standard protein; 344 AA.
XX
AC AAR93797;
XX
DT 16-SEP-1998 (first entry)
XX
DB Protein LP40, a variant of OmpA protein P40 from K. pneumoniae I-145.
XX
KW Outer membrane protein; OmpA; P40; immunocomplex; oligosaccharide;
KW polysaccharide; vaccine; Salmonella.
XX
OS Synthetic.
OS Klebsiella pneumoniae.
XX
PN WO9741888-A1.
XX
PD 13-NOV-1997.
XX
PF 06-MAY-1997; 97WO-FR00800.
XX
PR 07-MAY-1996; 96FR-0005692.
XX
PA (FABR ) FABRE MEDICAMENT SA PIERRE.
XX
PI Binz H, Haeuw JF, Svenson S;
XX
DR WPI; 1997-558694/51.
DR N-PSDB; AAV13868.
XX
PT Immunogenic complex for use in anti-bacterial vaccine - comprises
PT bacterial oligo- or polysaccharide coupled to a Gram-negative
PT bacterial outer membrane protein or a Streptococcal HSA binding
PT protein
XX
PS Claims 11,12,20; Page 38-39; 63pp; French.
XX
CC The patent discloses a new immunogenic complex which consists of (1) an
CC oligo- or polysaccharide found naturally on bacteria, coupled to (2) a
CC carrier protein chosen from (a) the human serum albumin binding protein
CC of Streptococcus, (b) Gram-negative bacterial outer membrane proteins
CC (Omp), or (c) fragments of these proteins. The immunogenic complex is
CC useful in a vaccines to protect animals against infection by Salmonella,
CC especially those belonging to antigenic specificity group O:9,
CC including S. enteritidis, S. panama and S. dublin. A vaccine prepared
CC using an oligosaccharide from S. enteritidis can be used to provide
CC protection against septicaemia caused by S. typhi and against typhoid
CC fever, as well as to protect humans and animals from toxic infections
CC and zoonosis caused by Salmonella of the same serogroup. The carrier
CC proteins enhance the immunogenicity of the oligo- or polysaccharide
CC antigens. Inclusion of additional Salmonella capsule antigens, such as
CC the Vi antigen, increases the vaccine's efficacy against encapsulated
CC bacteria. The present sequence, protein LP40, is a preferred example of
CC a carrier protein which can be used in the immunocomplex. It is
CC obtained by recombinant expression of a modified Kleb. pneumoniae I-145
CC P40 gene in E. coli.
XX
SQ Sequence 344 AA;

Query Match 99.4%; Score 342; DB 18; Length 344;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 342; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy       1 MKAIFVLNAAPKDNTWYAGGKLGWSQYHDTGFYGNGFQNNNGPTRNDQLGAGAFGGYQVN 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 MKAIFVLNAAPKDNTWYAGGKLGWSQYHDTGFYGNGFQNNNGPTRNDQLGAGAFGGYQVN 60

Qy      61 PYLGFEMGYDWLGRMAYKGSVDNGAFKAQGVQLTAKLGYPITDDLDIYTRLGGMVWRADS 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 PYLGFEMGYDWLGRMAYKGSVDNGAFKAQGVQLTAKLGYPITDDLDIYTRLGGMVWRADS 120

Qy     121 KGNYASTGVSRSEHDTGVSPVFAGGVEWAVTRDIATRLEYQWVNNIGDAGTVGTRPDNGM 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     121 KGNYASTGVSRSEHDTGVSPVFAGGVEWAVTRDIATRLEYQWVNNIGDAGTVGTRPDNGM 180

Qy     181 LSLGVSYRFGQEDAAPVVAPAPAPAPEVATKHFTLKSDVLFNFNKATLKPEGQQALDQLY 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 LSLGVSYRFGQEDAAPVVAPAPAPAPEVATKHFTLKSDVLFNFNKATLKPEGQQALDQLY 240

Qy     241 TQLSNMDPKDGSAVVLGYTDRIGSEAYNQQLSEKRAQSVVDYLVAKGIPAGKISARGMGE 300
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     241 TQLSNMDPKDGSAVVLGYTDRIGSEAYNQQLSEKRAQSVVDYLVAKGIPAGKISARGMGE 300

Qy     301 SNPVTGNTCDNVKARAALIDCLAPDRRVEIEVKGYKEVVTQP 342
          ||||||||||||||||||||||||||||||||||||||||||
Db     301 SNPVTGNTCDNVKARAALIDCLAPDRRVEIEVKGYKEVVTQP 342
```